R_1 Correction for Quantitative Amide Proton Transfer Imaging

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Target audience: Researchers interested in the origins and applications of CEST imaging *in vivo*.

Purpose: Amide proton transfer (APT) imaging has been suggested as a surrogate biomarker of endogenous mobile proteins and peptides in biological tissues. However, conventional APT analyses using magnetization transfer asymmetry[1] (MTR_{asym}), may be significantly influenced by various confounding effects, such as non-specific magnetization transfer (MT), asymmetry in the MT line-shapes, water longitudinal relaxation (R_1) and direct saturation. These confounding influences need to be reduced for accurate quantification of APT contrast *in vivo*. Previously reported *in vivo* R_1 correction approaches[2] are based on a simplified two-pool (water and amide protons) model, in which a single, overall observed R_1 (R_{1obs}) of water is used to correct data. However, in biological tissues, water exists in multiple compartments (e.g. intracellular, extravascular extracellular and vascular spaces), and relaxation in each compartment is likely different. This heterogeneity may invalidate the corrections applied. In this study, Gd-DTPA was introduced into tissue in order to selectively alter extracellular relaxation in tumors. By such a means, the accuracy of R_1 corrections for APT imaging was evaluated *in vivo*.

Methods: *Theory*: Conventional APT contrast, MTR_{asym}, is defined as $MTR_{asym}(3.6\ ppm) = Z(-3.6\ ppm) - Z(3.6\ ppm)$, where Z is the water signal when the RF saturation is applied at a specific offset. An alternative three-offset method[3] was proposed to reduce asymmetric MT effects, namely $APT^*(3.6\ ppm) = [Z(4.2\ ppm) + Z(3\ ppm)]/2 - Z(3.6\ ppm)$. Combining the three-offset method with a reciprocal Z-spectrum analysis, a metric called the apparent exchange dependent relaxation (AREX) has been developed to correct for multiple confounding effects: $AREX^*(3.6\ ppm) = [1/Z(3.6\ ppm) - 2/(Z(4.2\ ppm) + Z(3\ ppm))]\cdot R_{1obs}$.

Experiments: MR images of male Wistar rats (340 – 380 g) bearing C6 brain tumors were acquired with a Varian 9.4T horizontal bore system. Fig. 1 shows the data acquisition protocol overlaid on spoiled-gradient echo (SPGR) signals. R_{1obs} was measured with a selective inversion recovery sequence. APT images were acquired with 5-sec CW saturation pulses at B_1 = 1 μT and offsets (ppm) = 300, 4.2, 3.6, 3, -3.6, -300. The SPGR sequence was used to monitor R_1 changes during and after Gd-DTPA (0.07 mmol kg^{-1}) intravenous injection. The above procedures, including the injections and acquisitions, were interleaved and repeated for four times to obtain higher accumulated R_1 changes. After pixel-by-pixel mapping of R_{1obs}, MTR_{asym}, APT*, and AREX*, quantitative analyses were performed on regions of interest (ROIs) of the tumors.

Results: Fig. 2 summarizes the correlations between APT contrasts (APT*, AREX*, MTR_{asym}) and R_{1obs} obtained *in vivo*. APT* appears to be significantly inversely correlated with R_{1obs} (Spearman's correlation $p < 0.001$), but after correction for R_1 relaxation, AREX* has no significant correlation with R_{1obs} ($p = 0.103$). Interestingly, MTR_{asym} also shows no correlation with R_{1obs} ($p = 0.873$).

Conclusion and Discussions: The significant dependence of APT* on R_{1obs} shows that it is necessary to perform R_1 correction for accurate APT imaging. The intracellular exchange lifetime has been reported to be ~ 600 ms, which is much shorter than the saturation pulse duration (5 sec). The integrated water signal from all spaces may then be approximately regarded as from a single water pool. Therefore, though Gd-DTPA selectively alters the extracellular space R_1, the overall observed R_1 (R_{1obs}) is still suitable for R_1 correction of APT imaging in biological tissues. The apparent independency of MTR_{asym} on R_{1obs} is unclear, and one possible explanation is the strong contamination by nuclear Overhauser enhancement (NOE) around - 3.5 ppm.

References: (1) Zhou J, Payen JF, Wilson DA, Traystman RJ, van Zijl PC. Nat. Med. 2003;9(8):1085-1090. (2) Xu J, Zaiss M, Zu Z, Li H, Xie J, Gochberg DF, Bachert P, Gore JC. NMR Biomed. 2014;27(4):406-416. (3) Jin T, Wang P, Zong X, Kim SG. Magn. Reson. Med. 2013;69(3):760-770.

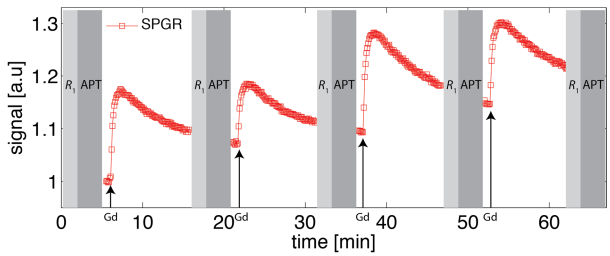

Fig. 1 Schematic of the data acquisition protocol.

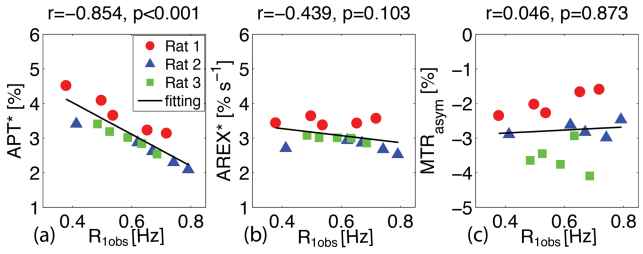

Fig. 2 Correlations of APT* (a), AREX* (b), and MTR_{asym} (c) with R_{1obs} for three rats. The Spearman's rank correlation coefficient (r) and p value are shown. The full lines represent the linear regression of all data points in each correlation subfigure.